REMARKS

Claims 1-9 are pending and under consideration in the instant application. With this response, Claim 1 has been amended. After entry of the instant amendment, Claims 1-9 are pending and under consideration. A version with markings to show changes made is attached at Exhibit A. For the Examiner's convenience, a clean copy of all pending claims is attached at Exhibit B.

I. THE AMENDMENT OF THE CLAIMS

Claim 1 has been amended to more particularly point out and distinctly claim the invention. In particular, Claim 1 has been amended to recite, in relevant part, that in the amplificates, "the sequences located between the binding sequences A and C contains no nucleotides that do not belong to a sequence E of the amplificate that is bound by binding sequence D of the probe." This clause points out a key aspect of the invention. Namely, the method is directed to detection of a target sequence by primer-mediated amplification of a 75 nucleotide or shorter segment of the target sequence taking place in the presence of a labeled probe sequence that binds all of the sequence between the two primer binding sites in the segment, wherein the detection signal is the label released from the probe sequence. Support for this amendment can be found, for example, in the specification, at page 26.

As the amendment is fully supported by the specification, it does not constitute new matter. Entry thereof is therefore respectfully requested.

II. THE REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-2, 4-5 and 9 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over a combination of U.S. Patent No. 5,538,848 ("Livak") in view of U.S. Patent No. 5,882,857 ("Western"). Claims 3 and 6-8 stand rejected as allegedly being unpatentable over Livak in view of Western. Applicants respectfully submit that the PTO has again failed to meet its initial burden of establishing a *prima facie* case of obviousness.

A. Legal Standard for Obviousness

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d. 1443, 1444 (Fed. Cir. 1992).

In order to establish *prima facie* obviousness, three basic criteria must be met. First, when an obviousness rejection relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. *In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside* , 53 USPQ2d 1769 (Fed. Cir. 2000). If any one of three criteria are not met, *prima facie* obviousness is not established. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

B. The References Cited by the PTO Fail to Teach Each and Every Element of Claims 1-9

Amended Claim 1 recites a method for the detection of a nucleic acid comprising producing 75 nucleotide or shorter amplificates of the nucleic acid using two primers, a polymerase have 5' nuclease activity and a labeled probe sequence, and detecting a signal from label released from the probe sequence, wherein the amplificate sequence between the two primer binding sites contains no nucleotides that do not belong to a sequence region E that is bound by binding sequence D of the probe. Claims 2-9 depend from amended Claim 1.

Applicants submit that the prior art cited by the PTO does not teach or suggest each and every element of Claim 1. In particular, the claimed method involves release of label from the probe during amplification of a 75 nucleotide or smaller amplificate, wherein the amplificate sequence between the two primer binding sites contains no nucleotides that are not bound by binding sequence D of the probe. That is, the claimed method involves label

release from a probe sequence that binds to all of the sequence between the two primer binding sites during the amplification of a small amplificate (*i.e.*, 75 nucleotides or shorter in length). As further taught by the specification, the probe binding sequence D may or may not overlap with the primer binding sites. (*See,* page 26 and Fig. 3I-VI). Neither Livak nor Western, alone or in any combination, teaches or suggests Applicants' claimed method.

The PTO asserts that Livak teaches amplification reactions involving two primers and a labeled probe that hybridizes between the two primer sites. The PTO admits that Livak does not teach reactions that produce amplificates of 75 nucleotides or shorter. The PTO asserts, however, that Western *teaches* "an amplification product of 30-5000 nucleotides, which is capable of hybridizing to a probe." The PTO further asserts that it is well established that polymerases are capable of binding and extending nucleic acids smaller than 75 nucleotides in length while bound to a probe.

Applicants respectfully disagree with several of these assertions and their reputed significance. In the first instance, Western provided no evidence that small amplificates (*e.g.*, 75 nucleotides or shorter in length) can indeed be made. Thus, at best Western suggests that *might be possible*. Further, Western's alleged suggestion that short sequences can hybridize to a probe in no way suggests the desirability or more significantly, the possibility of amplifying short sequences in the presence of a probe sequence that binds to all of the sequence between the two primer sites. Indeed, the PTO has not provided prior art that teaches or suggests a polymerase can bind and extend nucleic acids on a 75 nucleotide or shorter amplificate while the latter is bound to a probe sequence that covers all of the region between the two primer binding sites. In fact, the cited art, Livak and Western, also do not teach or suggest that a polymerase can degrade a probe sequence which is bound immediately adjacent to a primer on an amplificate that is 75 nucleotides or shorter in length. Accordingly, the PTO has failed to establish a *prima facie* case of obviousness against the claimed invention because neither Livak nor Western, alone or in any combination, teaches or suggest each and every element of Claims 1-0.

Even assuming *arguendo* that Livak and Western suggest the claimed method, these references however, provide no reasonable basis for expecting success of the claimed method (*i.e.* a polymerase amplifying a 75 nucleotide or shorter amplificate that has a probe sequence bound immediately adjacent to a primer binding site, and degrading the probe sequence to

release a labeled nucleotide). Indeed, Western suggests the claimed method might not work. Specifically, Western teaches that the efficiency of an amplification reaction is reduced when a non-primer oligonucleotide (*e.g.* probe sequence) binds within or near a primer binding site, *see*, Column 13, lines 54-61. That is, Western would have led an ordinary artisan to doubt the ability of Applicants' claimed method to produce sufficient amount of amplificate and the associated label release to enable detection.

Based on all of the foregoing Applicants respectfully submit that Livak and Western do not render Applicants' claimed invention obvious. Applicants therefore request that the rejection of Claims 1-9 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Applicants submit that Claims 1-9 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-9 to issuance is therefore kindly solicited.

No fees in addition to the fee for Request for Continued Examination are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP U.S. Deposit Account No. 16-1150.

Respectfully submitted,

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EXHIBIT A
Claim Amendment: Version with Markings to Show Changes Made

1. (Four times amended) A method for the detection of a nucleic acid comprising [the steps]:

(a)- producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which can bind to a first binding sequence [(A)] A of one strand of the nucleic acid and the other can bind to a second binding sequence [(C')] C' which is essentially complementary to a sequence C which is located in the 3' direction from A and does not overlap A, in the presence of a probe [with] having a binding sequence D which can bind to a third sequence [(B)] B located between the sequences A and C or to the complement [(B')] thereof, wherein the probe contains a reporter group and a quencher group, using a polymerase having 5' nuclease activity [,] ; and

(b)- detecting the nucleic acid by measuring a signal which is caused by the release of the reporter group, wherein the amplificates have a length of [less than] 75 nucleotides or less, and the sequence located between the binding sequences A and C contains no nucleotides that do not belong to a sequence region E of the amplificate that is bound by binding sequence D of the probe.